Internal and Emergency Medicine (2019) 14:1341–1346
https://doi.org/10.1007/s11739-019-02175-4

CE - RESEARCH LETTER TO THE EDITOR

Randomized trial of two after-dialysis gabapentin regimens for severe uremic pruritus in hemodialysis patients

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Received: 17 May 2019 / Accepted: 11 August 2019 / Published online: 7 September 2019

Uremic pruritus (UP) has an overall reported incidence of ~46% in patients on hemodialysis, and is a relevant issue in the management of CKD [1, 2]. Gabapentin seems to be the best available treatment option, but since it is mainly eliminated by the kidneys, neurotoxicity is a concern, and sleepiness is the most frequently reported adverse reaction in clinical trials [2].

In this randomized, double-blind, placebo-controlled trial of gabapentin in hemodialysis patients with UP, we sought to determine the efficacy of two fixed-dose, after-dialysis drug regimens versus placebo.

Patients on thrice-weekly hemodialysis who met the following criteria were included: (1) age above 18 years; (2) history of itch for more than 6 weeks as per the definition of chronic itch by the International Forum for the Study of Itch [3]; (3) female subjects had to be willing to use adequate contraception; (4) a negative serum pregnancy test at initial screening of female subjects with childbearing potential.

Exclusion criteria were as follows: (1) history of itch preceding kidney failure; (2) dermatologic conditions causing pruritus (e.g., atopic dermatitis, allergy); (3) hypereosinophilia (eosinophil count > 500/mm^3) and/or serum IgE elevation (> 120 UI/mL); (4) elevated calcium–phosphorus product (> 60 mg^2/dL^2); (5) elevated serum biliary acids (> 6 µmol/L); (6) Kt/V < 1 (calculated with the equivalent renal clearance method) [4]; (7) treatment with glucocorticoids, opioids, anti-histamines and other potentially interfering therapy (e.g., ultraviolet therapy); (8) hypersensitivity to any of the components of the study drug; (9) active alcohol or drug abuse or history of such abuses in the preceding 6 months; (10) any of the following comorbidities: cholestasis, neoplasia, rheumatic diseases.

The study protocol was approved by the Azienda Ospedaliera Santa Maria Nuova (Reggio Emilia, Italy) ethical committee and registered on the European Union Clinical Trials Register with the number 2009-010437-50 (https://www.clinicaltrialsregister.eu/ctr-search/trial/2009-010437-50/IT). All patients signed their informed consent prior to study enrolment.

At the time the study protocol was written, our pilot study and available data from the literature showed that gabapentin treatment resulted in > 50% itch reduction, assessed as mean percent decrease in the visual analog scale score (VASS) for pruritus, compared to placebo; mean VASS and standard deviations for the gabapentin and placebo groups were derived from the aforementioned studies, and an a priori sample size calculation for repeated-measures *t* test [5] with a two-tail significance level of 5% and with 90% power was performed; a required sample size of eight patients per study group was thus calculated [6–8].

Visual analog scales (VAS) are used to measure symptom severity in a wide variety of disorders. They usually consist of a 10 cm or 100 mm scale, with 0 being the absence of the symptom and 10 cm or 100 mm its most intense expression. The patient is asked to provide a "graphic" rating of the symptom severity by choosing the most appropriate point in the scale. VAS have been transitioned to UP studies [9] from trials on the pharmacological management of pain, a setting in which they have been employed for several years now [10]. A VAS for pruritus, with 0 mm being no itch

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and 100 mm being the worst imaginable itch, was administered to eligible patients after each dialysis session (DS) for a week. Patients with a mean VASS > 50 mm, which was our arbitrary definition of severe UP, were randomly assigned by the designated pharmacist to one of three treatment groups according to a computer-generated randomization code, using blocked randomization with randomly selected block sizes. The three treatment groups were gabapentin 100 mg, gabapentin 300 mg, and a matching placebo, manufactured by the hospital pharmacy (identical appearance, taste, size). Gabapentin 100 mg, 300 mg, and placebo tablets were blinded to patients, physicians and nurses, and were administered after each DS for 2 weeks. A VASS and a sleep disturbance questionnaire adapted from a previous work [11] were also administered after each DS during the 2 weeks of therapy and a week after therapy withdrawal. The results of VASS and sleep disturbance questionnaires from previous DS were not shown to patients on subsequent DS.

The primary objective was the percent change in VASS (compared between treatment arms) from baseline to day 14; secondary end-points included sleep disturbance outcome measures (i.e. nocturnal scratching episodes, waking-up episodes) and treatment-related toxicity. Adverse reactions were graded according to CTCAE v4.0 [12].

The sleep disturbance questionnaire was scored as follows: any episode of waking up due to itch received 2 points (maximum 10 points) and each scratching episode with or without excoriation during the night received 1 point (maximum 5 points). These two scores were analyzed individually and as a composite outcome which was the numerical sum of the two. The percent change in VASS was compared between groups using the Mann–Whitney test.

Itch reduction for each group, measured as a change in absolute VASS before and after treatment (from day 0 to 14), and the sleep disturbance outcome measures for each group, before and after treatment (from day 0 to 14), were evaluated with Wilcoxon matched-pairs signed-rank test. One-way ANOVA was used to test treatment groups for differences in baseline characteristics. All statistical analyses were performed using Graphpad Prism 7; p values < 0.05 were considered statistically significant.

Twenty-five patients were enrolled. Patients' characteristics at baseline and differences between treatment groups are listed in Tables 1 and 2, respectively. Four patients were excluded as they refused taking the drug after randomization. Of the remaining 21, 5 were in the 300 mg arm, 8 in the 100 mg arm and 8 in the placebo arm. Two patients developed neurological impairment in the form of excessive sedation (lethargy) respectively at days 9 and 10 of treatment; both adverse events were CTCAE grade 4. The treatment allocation of these two patients was then unmasked for safety concerns: both of them were in the 300 mg arm. Enrolment in this arm was no longer continued. 300 mg pills were unmasked and discarded by the designated pharmacist. Blinding was maintained thereafter, the patients being randomized only to gabapentin 100 mg or placebo.

Itch reduction, measured as a change in the absolute VASS from day 0 to day 14, was statistically significant in the 100 mg arm ($p = 0.0078$) but not in the 300 mg arm (presumably for the small number of patients that could be analyzed after enrolment in the latter arm was stopped) or in the placebo arm (Fig. 1a). No significant increase in VASS between day 14 and day 21 was observed in the three groups. A significant difference was observed in percent VASS reduction (day 14 vs. baseline) between the 100 mg and placebo, the 300 mg and placebo, the 300 mg and 100 mg arms (Fig. 1b).

Nocturnal scratching episodes did not significantly decrease in any of the groups, while waking up episodes due to itching significantly decreased only in the 100 mg arm ($p = 0.015$), as did the composite outcome of nocturnal scratching and waking up episodes ($p = 0.046$).

With respect to treatment-related toxicity, no adverse reactions were observed other than those reported above in the 300 mg arm.

UP is associated with impaired quality of life, depression, poor sleep quality and increased mortality. A recent systematic review of treatments for UP, including only randomized controlled trials, concluded that the best available evidence is that regarding gabapentin, even though larger-scale studies are still warranted [2]. Our results are in line with previous findings and confirm that an after-dialysis low-dose gabapentin regimen is effective and safe for UP, with benefits also on the quality of sleep. Our study has nonetheless several limitations, the most relevant being the small number of patients involved. To our knowledge, however, this is the first trial to compare two different after-dialysis fixed-dose gabapentin regimens in a parallel design. Nofal et al. [13] performed a single-blinded randomized placebo-controlled trial of gabapentin after-dialysis in 54 patients with UP on thrice-weekly hemodialysis, with gabapentin being titrated to effect to a maximum allowed dose of 300 mg. Dizziness, somnolence and fatigue were observed in 18.5%, 11.1% and 3.7% of the patients, respectively. The Authors, however, did not report if the adverse events were more frequent in patients who received higher gabapentin doses. Other trials have compared high-dose gabapentin (300–400 mg after each DS) either with placebo [6, 8] or pregabalin [14] after-dialysis. Gunal et al. [6] performed a randomized double-blind placebo-controlled cross-over trial of gabapentin 300 mg after-dialysis in 25 patients with UP on thrice-weekly hemodialysis; patients were randomized either to gabapentin for 4 weeks and then placebo for 4 weeks, or the reverse treatment. Naini et al. [8] performed a randomized double-blind placebo-controlled trial of gabapentin 400 mg after-dialysis in 34 patients with

Table 1 Patients' baseline characteristics

Patient ID	Age	Gender	Study arm	Cause of end-stage renal disease	HD duration (months)	Relevant comorbidities	Serum creatinine (mg/dL)	Azotemia (mg/dL)	Mean Kt/V (previous month)	C-reactive protein (mg/L)	PTH (pg/mL)	Calcium (mg/dL)	Phosphorus (mg/dL)	Albumin (g/dL)
1	80	F	gaba 300 mg	Chronic tubulointerstitial nephritis (NSAIDs)	23	HTN, T2DM, IHD, AFib	11.2	152	1.38	3.06	588	9.4	3.9	4.4
2	78	F	gaba 300 mg	Chronic tubulointerstitial nephritis (unknown cause)	18	IHD, HTN, T2DM	5.58	142	1.8	0.23	41	10.1	5.1	3.9
3	61	F	Placebo	Polycystic kidney disease	96	HTN, IHD	9.4	160	1.09	0.09	1051	7.8	6.2	4.3
4	75	F	Placebo	Nephroangiosclerosis	26	IHD, COPD	7	96	1	0.15	11	9.5	5.3	4.2
5	61	F	Placebo	Proteinuric nephropathy not otherwise specified	471	AFib, HCV	7.9	94	2.29	0.72	43	7.7	2.6	3.2
6	70	M	gaba 300 mg	Diabetic nephropathy	231	T2DM, HTN	8.8	108	1.2	1.56	4	10	4.4	3.4
7	68	M	gaba 100 mg	Diabetic nephropathy	21	HTN, T2DM, BPH	13.2	200	1.1	0.1	197	9	5.7	4.3
8	50	M	gaba 300 mg	Nephroangiosclerosis	40	HTN	17.71	101	1.31	0.38	496	10.1	5.2	4.4
9	74	F	gaba 300 mg	Proteinuric nephropathy not otherwise specified	40	HFrEF	7.12	100	1.06	0.3	10.9	9.5	2.4	3.9
10	79	M	gaba 100 mg	Nephroangiosclerosis	50	HTN	9.48	53	1.17	0.24	233	7.9	4.2	3.9
11	71	F	Placebo	Diabetic nephropathy	1	HTN, T2DM	6.83	158	1.15	0.74	154	8.4	4.7	3
12	54	F	gaba 100 mg	IgA nephropathy	3	HTN	8.69	144	1.5	1.06	393	8.7	4.9	3.9
13	76	M	Placebo	Nephroangiosclerosis	4		7.6	161	1.1	24	103	7.9	3.8	3.2
14	38	M	gaba 100 mg	Focal segmental glomerulosclerosis	32		16.2	194	1.5	0.56	450	8.3	5.9	3.8

Table 1 (continued)

Patient ID	Age	Gender	Study arm	Cause of end-stage renal disease	HD duration (months)	Relevant comorbidities	Serum creatinine (mg/dL)	Azotemia (mg/dL)	Mean Kt/V (previous month)	C-reactive protein (mg/L)	PTH (pg/mL)	Calcium (mg/dL)	Phosphorus (mg/dL)	Albumin (g/dL)
15	76	F	gaba 100 mg	Nephroangiosclerosis	20		6.4	148	1.8	7.78	500	8.8	4.7	3.9
16	66	M	gaba 100 mg	Polycystic kidney	156	HTN, HCV	8.5	148	1.3	0,5	250	8.7	4.8	3.4
17	71	F	Placebo	Polycystic kidney	135	HTN	8.6	103	1.7	3.51	470	9.1	3.8	4.1
18	49	M	gaba 100 mg	Not known	111		10.9	74	1.5	1.29	288	9.5	5.1	4
19	70	M	Placebo	Nephroangiosclerosis	1	HTN	5.3	73	1.2	25.8	262	8.2	5.1	3.2
20	31	F	gaba 100 mg	Lupus nephritis	26	HTN	7.3	170	1.8	2.4	190	9	5.1	4.1
21	26	F	Placebo	Diabetic nephropathy	41	HTN	4.2	117	2	2.7	497	8.1	5.1	3.9

gaba gabapentin, *NSAIDs* non-steroidal anti-inflammatory drugs, *HTN* hypertension, *T2DM* type 2 diabetes mellitus, *IHD* ischemic heart disease, *AFib* atrial fibrillation, *COPD* chronic obstructive pulmonary disease, *HCV* hepatitis C virus, *BPH* benign prostatic hyperplasia, *HFrEF* heart failure with reduced ejection fraction

UP on twice-weekly hemodialysis; patients received treatment or placebo for 4 weeks. Solak et al. [14] performed a 14-week long randomized trial of gabapentin 300 mg versus pregabalin 75 mg in 50 patients on thrice-weekly hemodialysis; patients were randomized to 6 weeks of either treatment followed by a 2 week-long wash-out and then 6 weeks of the other treatment. Despite differences in trial design, all these studies relied on VASS as an outcome measure for pruritus and found gabapentin to be effective in UP; the mean % VASS reduction attributable to gabapentin treatment ranged from 44 to 67%, which is in keeping with our findings [6, 8, 13, 14]. Somnolence and dizziness were reported as common side effects in these works, but only in the paper by Solak [14], the event rates were reported (15% and 12.5%, respectively). Moreover, the severity of these events was not graded with widely accepted adverse event grading systems. Mild or moderate somnolence might indeed have been severe drug-related adverse events.

Although our study was underpowered to draw conclusions about the frequency of gabapentin-related adverse events, the severity of those we observed in the 300 mg arm invokes caution in gabapentin prescription and reaffirms the necessity for a step-wise dose-escalation of the drug [15], balancing its efficacy with tolerability in the individual patient. Indeed, a key finding of our study is that as little a dose as 100 mg after-dialysis is effective, which is not only supportive of a gabapentin dose-escalation approach but potentially also of a combination approach with topical treatment, thus sparing higher gabapentin doses and the inherent increased risk of neurotoxicity, in a similar fashion to what is common practice in the pharmacological management of pain (e.g., opiod and non-steroidal anti-inflammatory drugs combination regimens). Interestingly, we did not find any benefit on nocturnal scratching, despite a decrease in waking up episodes, irrespective of the drug dose. We cannot exclude that this reflects itching due to skin lesions from chronic scratching rather than from UP itself, suggesting again a role for add-on topic treatments; nor our cohort was large enough to study separate effects of gabapentin on restless legs syndrome (which might benefit from low drug doses, herein the decrease in waking up episodes) and nocturnal UP. Another unexplored issue is whether treatment efficacy is maintained over time; despite clinical practice indicating so, and clinical trials showing that upon withdrawal of the drug the effect rapidly vanishes [14], this has not been formally addressed in an experimental setting. Hopefully, future clinical trials on larger cohorts with extended follow-up will shed definitive light on these aspects.

Table 2 Demographic and dialysis-related characteristics of the patients enrolled in the three treatment arms

	Gabapentin 100 mg	Gabapentin 300 mg	Placebo	*p* value
n	8	5	8	
F	3	3	6	0.314
Age (years)	60 (31–79)	74 (50–80)	70 (26–76)	0.387
Dialysis vintage (months)	29 (3–156)	39 (18–231)	33 (1–471)	0.389
PTH (pg/mL)	269 (190–500)	41 (4–588)	208 (11–1051)	0.802
Kt/V	1.5 (0.8–1.8)	1.3 (1.0–1.8)	1.1 (0.9–2.29)	0.836

All values except for gender and total patient number are reported as median and range

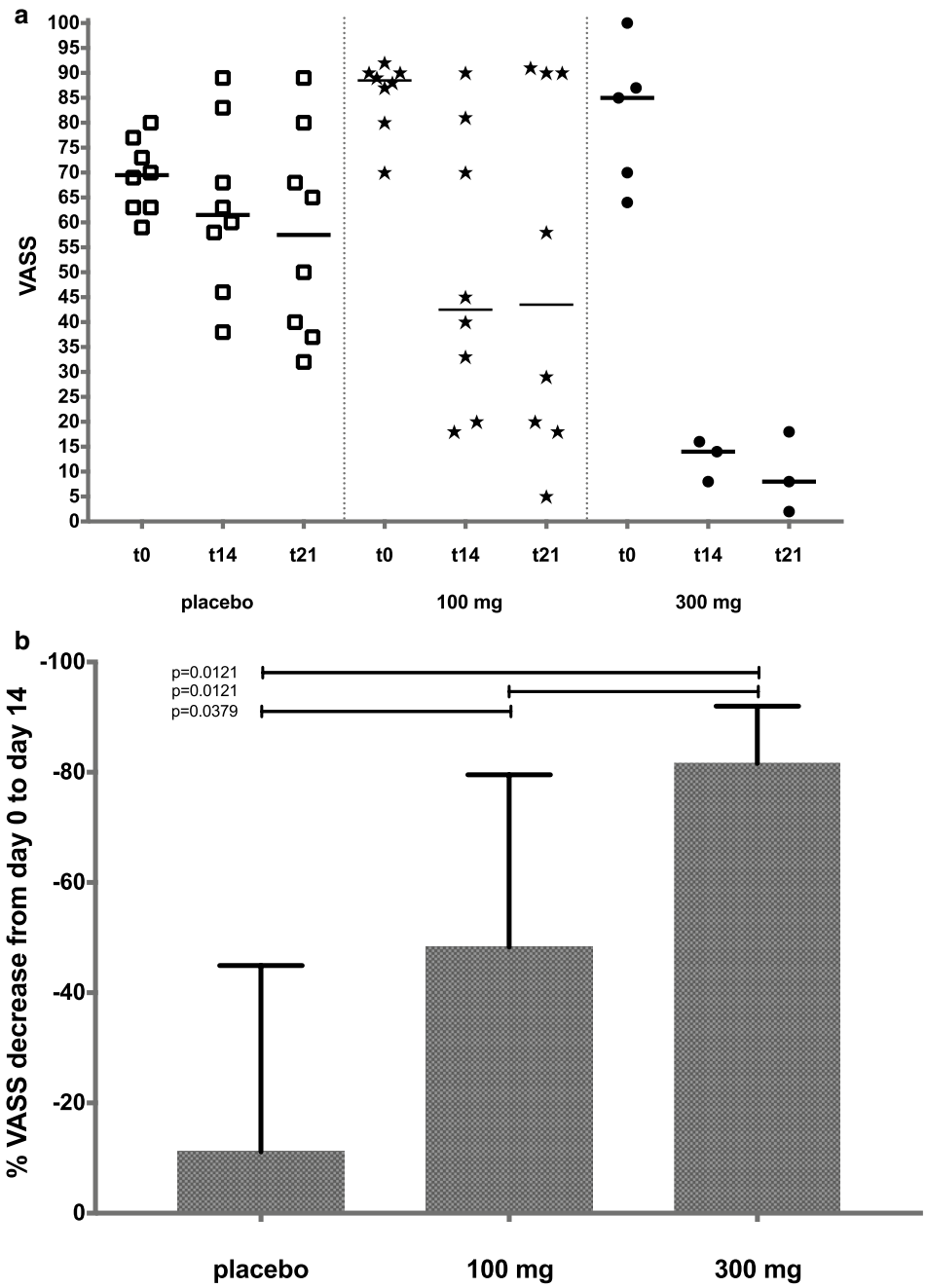

Fig. 1 Changes in Visual Analog Scale scores induced by gabapentin treatment. **a** Dot plots of Visual Analog Scale scores (VASS) (*Y* axis) at different time points in the three study arms (gabapentin 100 mg, gabapentin 300 mg, and placebo). Horizontal lines show the median VASS. At baseline, the median VASS was 88.5 mm (range 70–92 mm), 84 mm (range 64–100 mm) and 69.5 mm (59–80 mm) in the 100 mg, 300 mg and placebo arms respectively. After 2 weeks, in the same arms, the median VASS was respectively 42.5 mm (range 18–90 mm), 14 mm (range 8–16 mm) and 61.5 (38–89 mm). At day 14, i.e. after 2 weeks of therapy, 3/8 patients (37.5%) in the 100 mg arm, 5/5 patients (100%) in the 300 mg arm and none in the placebo arm had achieved a VASS reduction ≥ 50%. A week after drug withdrawal (t_{21}), median VASS in the 100 mg, 300 mg and placebo arms were as follows: 43.5 mm (range 5–91 mm), 8 mm (range 2–18 mm), 57.5 mm (range 32–89 mm). **b** Median percent VASS decrease from day 0 of treatment to day 14, with range error bars. Median percent VASS decrease was compared between groups using the Mann Whitney test; *p* values are reported. The median percent VASS variation after 2 weeks of treatment was − 48.3% in the 100 mg arm, − 81.61% in the 300 mg arm, − 11.11% in the placebo arm

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Statement of human and animal rights All procedures were approved by the Azienda Ospedaliera S. Maria Nuova of Reggio Emilia Ethical Committee, and were compliant with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent All participants provided informed consent prior to their participation.

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